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Nimodipine disposition and haemodynamic effects in patients with cirrhosis and age-matched controls

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1 Six biopsy proven cirrhotics and five age-matched controls (mean 55.3 *vs* 52.4 years) were randomly given single 60 mg p.o. and 30 mg s.l. doses of nimodipine. Serum concentrations and blood pressure were measured regularly over the subsequent 24 h period.

2 The clearance of nimodipine was reduced in the patients with cirrhosis. Apparent oral clearance of nimodipine in the cirrhotic group was significantly lower than that observed in the normal group (187 ± 163 l h^{-1} *vs* 469.6 ± 198.4 l h^{-1}, $P < 0.01$).

3 There were no significant changes in mean arterial pressure (MAP) in the normal subjects. There were, however, significant reductions in MAP following oral nimodipine in the cirrhotics. These reductions were significantly related to nimodipine concentrations in individual patients ($P < 0.05$).

Keywords calcium channel blockers liver disease pharmacodynamics pharmacokinetics

Introduction

Nimodipine is a 1,4 dihydropyridine which inhibits vascular smooth muscle contraction by inhibiting the influx of extracellular calcium through calcium channels. Several independent investigators have shown nimodipine to possess potent activity in cerebrovascular tissue at concentrations that elicit little or no activity on systemic vascular smooth muscle (Towart & Kazda, 1979; Towart *et al.*, 1982; Peroutka *et al.*, 1984). This relative selectivity has permitted trials of nimodipine in the prevention and reduction of cerebrovasospasm following acute aneurysmal subarachnoid haemorrhage (Allen *et al.*, 1983). This was not possible with previously available calcium channel antagonists since the hypotensive action of less selective agents might actually precipitate cerebrovasospasm (Wijdicks *et al.*, 1985).

The mechanism by which nimodipine improves the neurologic outcome following subarachnoid haemorrhage remains much debated (Allen *et al.*, 1983; Espinosa *et al.*, 1984; Weir, 1984). However, the cerebrovascular specificity of nimodipine, when demonstrated *in vitro*, appears to be a concentration dependent phenomenon (Haws *et al.*, 1983). The patient population who will receive nimodipine will include some with impaired hepatic function. The primary route of nimodipine elimination is hepatic oxidation of the dihydropyridine nucleus to a pyridine moiety (Meyer *et al.*, 1983). Patients with hepatic impairment, such as cirrhosis, might be expected to

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have a reduced clearance of nimodipine. Reduced clearance of a structurally related dihydropyridine drug, nitrendipine, was observed in patients with hepatic impairment (Lasseter *et al.*, 1984). The purpose of this study is two-fold; to assess the influence of hepatic cirrhosis on the disposition of nimodipine, and also to determine whether the disease processes attendant to hepatic cirrhosis produce any functional change in the sensitivity of the systemic blood pressure to nimodipine when compared to a group of age matched controls.

Methods

A total of eleven subjects was studied, each on two occasions separated by a 7 day period. Six patients with biopsy-proven cirrhosis and five healthy, age-matched volunteers participated in the study. The healthy volunteers ranged in age from 42 to 68 years (mean 52.4 years), and the patients with cirrhosis ranged in age from 38–72 years (mean 55.3) years. None of the volunteers of patients had significant renal, respiratory, endocrine or cardiovascular impairment. Patients or volunteers were excluded if they were judged to have a significant bleeding disorder, unstable hypertension (diastolic > 110 mmHg), unstable angina or recent myocardial infarction (within 2 months), severe infection, were undergoing concomitant treatment with other calcium antagonists or were women of childbearing potential. All subjects were within 10% of ideal body weight. Neither patients nor controls required concomitant medications during the study. Institutional Review Board approval was obtained and written informed consent was given by each participant.

Baseline history and physical examination was performed on each of the patients and volunteers. Baseline laboratory studies done included complete blood count, serum chemistry profile, clotting profile, urinalysis, and electrocardiogram.

After an overnight fast and 60 min of relaxation in a supine position, a nimodipine dose of two 30 mg capsules orally or the contents of one 30 mg capsule sublingually was randomly administered to each participant. The sublingual dose was held under the tongue for 15 min without swallowing. After the 15 min 'absorption' period, all saliva was collected, the participants' mouth was rinsed with normal saline, and this too was collected. Blood samples were collected at 0, 0.16, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, 8.0, 10.0 and 24.0 h after drug administration. All urine was collected for the two 24 h study periods. Blood pressure was recorded at each blood sampling time, and patients were observed constantly for the first 4 h after being given the drug. During this time subjects remained in a supine position. Patients were allowed to eat a standardized, low-protein lunch after the 4 h blood sample was drawn. There was at least a 7 day washout period between doses of nimodipine.

Sample handling and assay procedure

Blood samples were drawn through an indwelling intravenous catheter into a glass syringe and transferred immediately into opaque glass tubes. Serum was stored in opaque polypropylene containers at −70° C until assayed.

Assay procedure

A capillary GC procedure involving a toluene extraction step and electron capture detection was used for analysis of nimodipine in serum. Similar procedures for analysis of nitrendipine and nimodipine in plasma and urine samples were previously reported (Kann *et al.*, 1984; Raemsch *et al.*, 1985).

An aliquot of serum (1 ml) was mixed with 0.5 ml aqueous solution of nitrendipine internal standard and 0.25 ml of 1 N NH_4OH. The mixture was extracted with 1.0 ml of toluene and 2 μl of toluene extract was injected in the splitless mode at 220° C onto a fused silica capillary column. The column was coated with a 0.25 micron film of 5% methylphenyl silicone liquid phase (SE-54).

The chromatographic elution required a temperature gradient of 180° C to 280° C (10° C min^{-1}) and 5% methane in helium carrier gas at 25 psi inlet pressure. A Varian model 6000 GC instrument with electron capture detector was used. The detector temperature was 330° C.

Calculation of nimodipine concentrations was based on peak height response ratios obtained with nimodipine and internal standard. Calibration curves or linear response factors were used to calculate nimodipine concentrations. The nimodipine detection limit of the procedure was about 0.2 ng ml^{-1}, and the coefficient of variation of the assay ranged from 2.9% at higher concentrations to 12.6% at lower concentrations.

Pharmacokinetic and pharmacodynamic calculations

Area under the serum concentration time curve (AUC) was determined by La Grange method of area analysis for each subject. The AUC was

then used to determine the apparent oral clearance from the following relationship (Caprani *et al.*, 1975; Rowland *et al.*, 1973).

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC}_{0-\infty}} \qquad \text{equation 1}$$

Nimodipine serum concentration data was also fitted by a triexponential expression with first order input, and biexponential decline using nonlinear regression analysis to obtain estimates of elimination rate constants (Metzler *et al.*, 1974).

Measurements of pharmacologic effect (changes in mean arterial blood pressure), were fitted to the following expression:

$$E = E\ (\text{no drug}) + \frac{(\text{Emax})}{(Cp50\% * C)} \qquad \text{equation 2}$$

Where E (no drug) is baseline blood pressure, (Emax)/*C*p50%) is the slope of the regression line and *C* is the nimodipine concentration measured at the time blood pressure was measured (Rakhit *et al.*, 1984). Where data sets are best described by a linear rather than sigmoidal function, explicit solutions for Emax and *C*p50% cannot be obtained, and the ratio of these parameters can be considered constant.

Statistical analysis

Concentrations of nimodipine in patients with cirrhosis and age-matched normals were compared at each time point using the Mann-Whitney U-test. Differences in mean arterial pressure from baseline in both groups were assessed using ANOVA, analysis of variance for repeated measures.

Results

Nimodipine disposition

As seen in Figure 1, nimodipine concentrations displayed an apparent biexponential decline following the 60 mg oral dose. Sublingual administration did not effect the fundamental shape of the concentration-time curve. Peak nimodipine concentrations in the control group averaged 80.2 ng ml^{-1} occurring at 0.7 h and 19.0 ng ml^{-1} occurring at 1.3 h following oral and sublingual dosing respectively. Peak concentrations in the cirrhotic group averaged 115.8 ng ml^{-1} occurring at 1.75 h and 12.4 ng ml^{-1} occurring at 2.6 h following oral and sublingual dosing respectively.

Nimodipine serum concentrations between the two groups were significantly different by

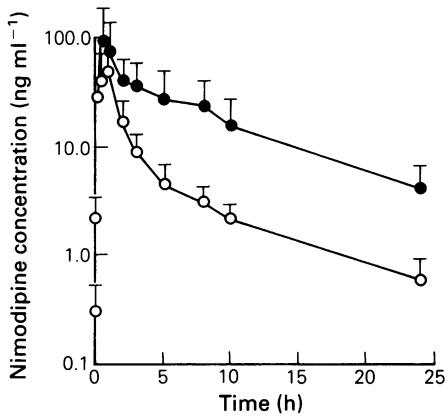

Figure 1 The time course of nimodipine serum concentrations (mean ± s.e. mean) following 60 mg oral dose in patients with cirrhosis (●) and age matched normal subjects (○).

Mann-Whitney U test at 2, 3, 8, 12 and 24 h after oral dosing and at 8, 12, and 24 h after a sublingual dose. Apparent clearance was greater in the age-matched controls than in the cirrhotics when given orally ($P < 0.05$) and when administered sublingually ($P < 0.05$). Neither the time required to achieve maximal concentrations nor the elimination rate constants in the cirrhotics were significantly different from those obtained in the control group.

Concentrations of nimodipine achieved after sublingual administration were much lower than those achieved after the 60 mg oral dose. Although 30 mg of nimodipine was placed under the tongue of each subject, the actual dose calculated by subtracting the amount of drug in the expectorated saliva from the original 30 mg, ranged from 8 mg to 18 mg. In both the normal and the cirrhotic group, apparent clearance after the oral dose did not differ substantially from the apparent clearance of the sublingual dose (Tables 1 and 2). There was no apparent difference in the urinary excretion of nimodipine or its metabolite following oral or sublingual dosing, but, less than 0.1% of the administered nimodipine dose was excreted unchanged in the urine of either group, precluding any additional insight from urinary data.

Changes in mean arterial pressure

There was no difference in systolic pressures (131 ± 8 mm Hg) of normal and cirrhotic subjects (127 ± 10 mm Hg) prior to the treatment. After administration of the oral dose, changes in mean arterial pressure were noted in most of the

Table 1 Individual pharmacokinetic parameters following oral administration of nimodipine

Patient	C_{max} *(ng ml^{-1})*	t_{max} *(h)*	*AUC (0−∞) (ng ml^{-1} h)*	λ_z *(h^{-1})*	*CL (l h^{-1})*	*Urinary recovery (%)*
Patients with liver disease (n = 6)						
1	93.9	0.5	296.5	0.074	203	—
6	25.3	1.0	92.0	0.068	652	0.003
7	158.9	0.52	284.2	0.074	211	0.004
9	250.9	0.5	892.0	0.055	67	—
10	95.6	3.0	539.6	0.154	111	0.0006
11	68.9	5.0	998.9	0.104	60	—
Mean ± s.d.	115.8 ±79.3	1.75 ±1.86	517.2 ±362.5*	0.088 ±0.36	217 ±222*	
Age matched normals (n = 5)						
2	58.5	0.76	114.5	0.063	524	0.0011
3	66.4	1.0	134.9	0.156	444	0.0008
4	84.5	1.0	166.0	0.071	361	0.0025
5	65.0	0.5	73.4	0.234	816	0.0005
8	126.5	0.25	133.2	0.090	451	0.0034
Mean ± s.d.	80.2 ±27.7	0.70 ±0.33	124.5 ±34*	0.122 ±0.72	519 ±176*	

*$P < 0.05$

Table 2 Individual pharmacokinetic parameters following sublingual administration of nimodipine

Patient number	*Actual dose (mg)*	C_{max} *(ng ml^{-1})*	t_{max} *(h)*	*AUC (0−∞) (ng ml^{-1} h)*	λ_z *(h^{-1})*	*CL (l h^{-1})*	*Urinary recovery (%)*
Patients with liver disease (n = 6)							
1	18	15.6	1.97	87.07	0.078	207	0.0009
6	15	8.9	1.0	61.25	0.044	245	0.001
7	16	17.9	1.0	64.49	0.078	248	0.003
9	8	11.5	1.0	83.44	0.045	96	—
10	10	7.7	10.0	100.66	0.12	99	0.0014
11	16	13.2	0.75	301.65	0.013	53	—
Mean ± s.d.		12.4 ±4	2.5 ±3.6	116.3 ±91*	0.063 ±0.037*	158 ±85*	
Age matched normal subjects (n = 5)							
2	12	18.2	0.75	42.8	0.129	280	0.0052
3	14	10.7	1.0	31.1	0.092	452	0.007
4	11	8.0	1.0	26.8	0.135	407	0.0014
5	13	4.6	0.75	16.6	0.131	778	—
8	15	53.6	3.06	81.8	0.089	183	0.0008
Mean ± s.d.		19.0 ±19	1.3 ±0.98	39.8 ±25*	0.115 ±0.022*	420 ±226*	

*$P < 0.05$

subjects over the course of the study day. The systolic blood pressure recordings in the cirrhotic group was significantly lower ($P < 0.05$) at 0.5 h (118 ± 4 *vs* 99 ± 11 mm Hg) and at 1.0 h (122 ± 8 *vs* 98 ± 12 mm Hg) after the oral nimodipine dose. In the control group, data from individual patients showed no systematic blood pressure changes and thus no relationship was found between nimodipine concentrations and change in mean arterial pressure (Table 3). The pooled

Table 3 Mean arterial blood pressure response to oral nimodipine

	Time (h)						
	0	*0.25*	*0.5*	*1.0*	*2.0*	*3.0*	*5.0*
Normal subjects	96.4	92.4	88.6	84.8	87.8	92.6	92.6
$n = 6$	±7.9	±5.9	±10.5	±12.4	±10.8	±6.5	±6.5
Liver disease	91.6	85.8	76.3*	76.1*	78.8*	82.3	82.5
$n = 5$	±12.1	±15.0	±14.5	±15.0	±14.0	±15.6	±9.7

*$P < 0.05$ ANOVA for repeated measures and Tukey's test.

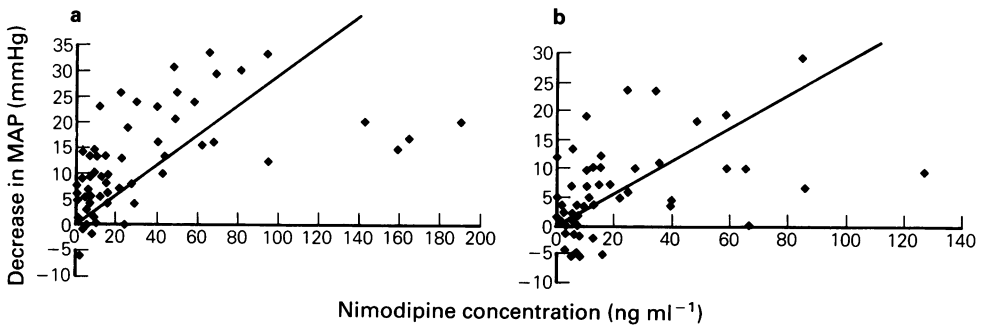

Figure 2 Nimodipine concentrations and changes in mean arterial blood pressure following 60 mg oral dose in patients with cirrhosis (a) and age matched normal subjects (b). The slopes of the two lines are identical (slope = 0.29).

control group data showed a weak but significant relationship between MAP and nimodipine concentrations as seen in Figure 2. In the group of patients with cirrhosis there was a consistent and significant decrease in mean arterial blood pressure which became evident 30 min after the oral nimodipine and persisted through the next 2 h. Blood pressure measured 3 h after the oral nimodipine was not different than baseline measurements in the cirrhotic group except in patients 9 and 11. Mean arterial pressures returned to baseline in these patients between 5 and 10 h after the oral dose. A significant relationship between MAP and nimodipine concentration could be demonstrated in five of the six cirrhotic patients, though the intersubject variability in the slope were large. Pooled data from the cirrhosis group also showed a significant relationship between MAP and nimodipine concentrations.

As seen in Figure 2, the slope of this curve (slope = 0.29, $r = 0.56$), was similar to that observed in the control group (slope = 0.29, $r = 0.47$). Following sublingual administration of nimodipine, no systematic effect on blood pressure was observed in either study group.

Discussion

The apparent oral clearance of nimodipine was significantly reduced, in the cirrhotic group when compared to the age matched controls. Due to the high intersubject variability, and small sample size, there were notable, but not significant increases in peak nimodipine concentrations, time to achieve peak concentrations, and terminal elimination rate constant in the cirrhotic patients.

This would be expected since nimodipine is highly metabolized, and data from normal subjects show it to be a high intrinsic clearance compound. There was a large variability in the influence of cirrhosis on nimodipine oral clearance, with values ranging from 60 l h^{-1} to 652 l h^{-1}. Like other highly protein bound, lipophillic compounds that are extensively metabolized, this variability in apparent oral clearance may be due to disease-induced changes in protein binding, gastric and enterohepatic absorption, and hepatic blood flow as well as intrinsic decreases in the metabolic capacity of the liver (Branch & Shand, 1976). Interestingly, the time course of nimodipine concentrations in two cirrhotic

patients (numbers 7 and 11) contained a marked second peak, at 4 h following the initial peak suggestive of enterohepatic recycling.

The relative contributions of each of these factors will require more detailed study in the specific patient populations. Clearly from these data, the disposition of nimodipine is altered in cirrhotic patients. Similar alteration of nitrendipine disposition in cirrhotic patients was also reported (Lasseter *et al.*, 1984).

It is interesting that sublingual administration of nimodipine did not result in any observed change in its disposition. It might be expected that sublingual absorption would circumvent first hepatic metabolism producing more rapid peak drug concentrations and a smaller clearance value (Metzler *et al.*, 1973; Rakhit *et al.*, 1984; Cleaveland & Shand, 1972). This was not seen in the present study. The time to reach peak nimodipine concentrations following sublingual administration was not different from the time to reach peak concentrations following oral dosing in either normal subjects or patients with cirrhosis. Clearances calculated following sublingual administration were markedly reduced in two subjects (numbers 6 and 2) but were very similar in the other nine subjects. The reason that apparent clearance of nimodipine was the same following oral and sublingual dosing is not clear. We have ruled out obvious sources of error. For example, great care was taken to prevent subjects from swallowing while the drug was on the sublingual mucosa, thus it is unlikely that the data are due to oral 'gastric' absorption. Also, nimodipine was held under the tongue without swallowing for as long as practically possible (15 min), and the amount of drug expectorated was accounted for in estimating apparent clearance. Finally, it is unlikely that absorption following oral administration was incomplete, yielding an underestimate of apparent clearance following the oral dose, since several studies have demonstrated rapid and complete gastric absorption of nimodipine using urinary recovery of radio labeled compound.

One possible explanation for the present data is that the nimodipine remained in the vehicle rather than be absorbed. Rinsing the oral mucosa with saline may not have been adequate to remove all of the vehicle containing nimodipine, and the residual was subsequently swallowed, producing the measured levels. Although this is speculative at best, it is clear that in its present formulation, there is no increased systemic availability following sublingual nimodipine administration.

The patients with cirrhosis exhibited greater changes in mean arterial blood pressure than did normal controls. There was a concentration related blood pressure reduction that could be seen in the individual data of cirrhotic patients, which was not evident in the individual control subjects. The only systematic nimodipine related blood pressure changes seen from the controls, was a weak but significant relationship in the pooled data.

Since the area under the nimodipine concentration curve in the cirrhotics was roughly four times that seen in normals, the more pronounced reductions in MAP would seem to be due to the greater nimodipine exposure. Consistent with this, the slope and intercept values of the nimodipine concentration:blood pressure reduction curves are the same for the pooled cirrhosis and pooled control subjects. Within the limitations of pooled data, there is no suggestion that cirrhosis alters the apparent vascular sensitivity to nimodipine. This paper reports a marked decrease in the apparent oral clearance of a single dose of nimodipine in patients with cirrhosis when compared to controls. Multiple dose long term studies will be needed to fully appreciate the mechanisms of reduced clearance as well as confirm the lack of disease influence nimodipine pharmacodynamics. The use of nimodipine sublingually in its present formulation does not appear to circumvent first pass metabolism.

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